AMENDMENT D

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(54) Title: SYNERGISTIC THERAPY WITH COMBINATIONS OF ANTI-TUMOR ANTIBODIES AND BIOLOGICALLY ACTIVE AGENTS

(57) Abstract

Methods of inhibiting tumor growth and development are described in which a combination of anti-tumor antibodies and biologically active agents, such as chemotherapeutic drugs, are utilized. The combination of anti-tumor antibody, such as the BR96 antibody, with a chemotherapeutic drug, such as doxorubicin or mitomycin C, is shown to produce a synergistic effect to inhibit tumor development and tumor cell growth.

agents. This has been recently reviewed for malignant melanoma, which is one of the human tumors most studied in this respect (Hellström and Hellström, in Accomplishments in Cancer Research-1984 Prize Year, General Motors Cancer Research Foundation, J.G. Fortner & J.E. Rhoads, eds., J. B. Lippincott Company, Philadelphia 1985, p. 216-240), as well as for other tumors (Burchell and Taylor-Papadimitriou, in R.W. Baldwin and V.S. Byers, eds., Monoclonal Antibodies for Tumor Detection and Drug Targeting, Academic Press, 1985, pp. 1-15; Kemshead, ibid, pp. 281-302.).

Many antibodies have been made to cell surface antigens that are expressed in greater quantities by human tumors than by normal tissues. It has also been well established that antibodies to cell surface antigens can be cytotoxic to tumor cells in the presence of complement (Hellström et al., 1962, Prog. Allergy 9:158-245), and that some antibodies can mediate antibody-dependent cellular cytotoxicity (Perlmann et al., 1969, Adv. Immunol. 11:117-193; MacLennan et al., 1969, Immunol. 17:897-910; Skurzak et al., 1972, J. Exp. Med. 135:997-1002; Pollack et al., 1972, Int. J. Cancer, 9:316-323). In the first case, an appropriate source of complement (generally rabbit or guinea pig), and in the latter case a source of effector cells (generally of mouse origin) is needed.

The evidence that antibodies to tumor-associated antigens can kill human tumor cells in the presence of human effector cells is more recent (Hellström et al., 1981, Int. J. Cancer 27:281-285) as is the evidence that antibodies to

such antigens can kill tumor cells in the presence of human serum as a source of complement (Hellström et al., 1985, Proc. Natl. Acad. Sci. 82:1499-1502; Hellström et al., 1985, Monoclonal Antibodies and Cancer Therapy, UCLA Symposia on Molecular and Cellular Biology, Vol. 27, pp. 149-164 Alan R. Liss, Inc., NY).

Therapeutic Uses of Anti-Tumor Antibodies As Carriers of Radioisotopes, Toxins or Drugs

Attractive approaches for preparing anti-cancer agents involve labeling antibodies with radioactive isotopes (Larson et al., 1983, J. Clin. Invest. 72:2101-2114; Order, 1984, Compr. Therapy 10:9-18; Carrasquillo et al., 1984, Cancer Treatment Reports 68:317-328; de Nardo et al., 1985, Int. J. Radiation Oncology Biol. Phys. 11:335-348), or conjugating antibodies to toxins (Jansen et al., 1982, Immunol. Rev. 62:185-216; Vitetta and Uhr, 1984, Transplant. 37: 535-538) or anti-cancer drugs (Ghose et al., 1972, Brit. Med. J. 3:495-449; Hurwitz et al., 1975, Cancer Res. 35:1175-1181; Rowland et al., 1985, Cancer Immunol. Immunother. 19:1-7). The antibody gives the specificity, and the isotope or drug provides the ability to destroy the tumor. However, a disadvantage of this approach is the fact that both anti-cancer drugs and radioisotopes have a high level of toxicity to normal tissues. Thus, nonspecific uptake in various organs such as kidney, liver, or bone-marrow could lead to substantial side-effects.